An update to this article is included at the end

Seizure: European Journal of Epilepsy 75 (2020) 145–152

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Medical management of status epilepticus: Emergency room to intensive care unit

Ania A. Crawshaw[a], Hannah R. Cock[b,*]

[a] Specialist Trainee Neurology, Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, UK
[b] Professor of Epilepsy & Medical Education, Consultant Neurologist. Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, and Institute of Medical & Biomedical Education, St George's University of London, London, UK

ARTICLE INFO

Keywords:
Status epilepticus
Treatment
Valproate
Levetiracetam
Benzodiazepines
Phenytoin

ABSTRACT

In convulsive status epilepticus (SE), achieving seizure control within the first 1–2 hours after onset is a significant determinant of outcome. Treatment is also more likely to work and be cost effective the earlier it is given. Initial first aid measures should be accompanied by establishing intravenous access if possible and administering thiamine and glucose if required. Calling for help will support efficient management, and also the potential for video-recording the events. This can be done as a best interests investigation to inform later management, provided adequate steps to protect data are taken. There is high quality evidence supporting the use of benzodiazepines for initial treatment. Midazolam (buccal, intranasal or intramuscular) has the most evidence where there is no intravenous access, with the practical advantages of administration outweighing the slightly slower onset of action. Either lorazepam or diazepam are suitable IV agents. Speed of administration and adequate initial dosing are probably more important than choice of drug. Although only phenytoin (and its prodrug fosphenytoin) and phenobarbitone are licensed for established SE, a now considerable body of evidence and international consensus supports the utility of both levetiracetam and valproate as options in established status. Both also have the advantage of being well tolerated as maintenance treatment, and possibly a lower risk of serious adverse events. Two adequately powered randomized open studies in children have recently reported, supporting the use of levetiracetam as an alterantive to phenytoin. The results of a large double blind study also including valproate are also imminent, and together likely to change practice in benzodiazepine-resistant SE.

1. Introduction

That status epilepticus (SE) requires emergency treatment has been embedded in practice for decades, and the 2015 ILAE definition [1] emphasises both the need for rapid initiation of treatment and the risk of permanent damage if seizures are not promptly controlled. There are however many types of SE, and it is recognized that outcome is also significantly influenced by seizure type and etiology, as well as the patient's age and comorbidities. In this review we will focus on the management of early and established convulsive SE for which there is most evidence to guide practice, though management of other types of SE will also be briefly discussed. The management of refractory SE, where seizures have not been controlled by first or second line treatment, is covered in a subsequent article in this supplement.

2. Does speed really matter?

It is widely acknowledged that age and etiology are the biggest determinants of outcome in SE. However, historical uncertainty about the influence of duration as an independent predictor has now been addressed by several large case series. It is clear that achieving seizure control within the first 1–2 hours of onset is a significant determinant of outcome [2] as summarized in Table 1. Systemic compromise [3], and brain damage, thought to be caused by a combination of direct damage from seizure-related activity and the secondary effects of the associated metabolic cascade, both contribute to morbidity and mortality. Furthermore, the earlier treatment of SE is instituted, the more likely it is to be successful. In one recent prospective study in children with refractory convulsive SE, benzodiazepine administration beyond the first 10 minutes was independently associated with a higher frequency of death, use of continuous infusions, longer convulsion duration, and hypotension [4]. Unsurprisingly prompt intervention, including pre-

* Corresponding author.
E-mail address: hannahrc@sgul.ac.uk (H.R. Cock).

https://doi.org/10.1016/j.seizure.2019.10.006
Received 30 March 2019; Received in revised form 7 October 2019; Accepted 8 October 2019
1059-1311/ © 2019 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

SHOUT
SHARE
IT

Table 1
Retrospective case series examining the influence of duration on outcome from convulsive status epilepticus.

Location year [ref]	Number of cases, age	Duration	% Poor outcome*
USA 1994 [6]	n = 253, >16y	< > 1 hour	**2.7 vs 32.0, OR 17.9**
Finland 1997 [7]	n = 65, <18y	< > 2 hours	**32.7 vs 68.8, p < 0.025**
Turkey 1998 [8]	n = 66, 6-77y	< > 1 hour	**3.0 vs 29.4, OR 2.41**
India 2005 [9]	n = 30, <18y	< > 45 mins	**9.5 vs 100.0, p < 0.001**
USA 2009 [10]	n = 119, 24-96y	< > 10 hours	31.0 vs 69.0, p < 0.05
Norway 2016** [11]	n = 56, 20-86y	< > 2 hours	**16.7 vs 52.3, OR 6.12**

Bold = multivariate analysis. OR = odds ratio; *death or significant disability; ** Refractory cases only, including 38 non-convulsive status epilepticus [2].

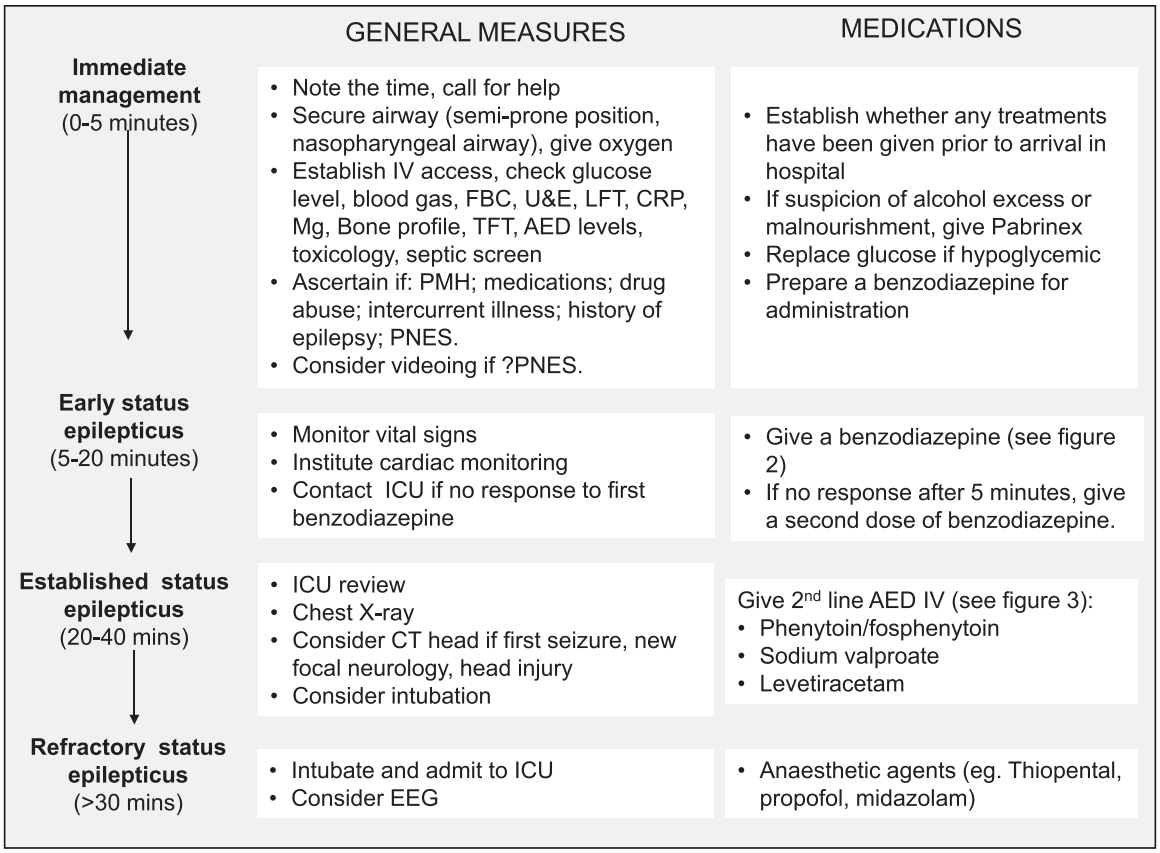
GENERAL MEASURES
MEDICATIONS
Immediate management (0-5 minutes)
• Note the time, call for help
• Secure airway (semi-prone position, nasopharyngeal airway), give oxygen
• Establish IV access, check glucose level, blood gas, FBC, U&E, LFT, CRP, Mg, Bone profile, TFT, AED levels, toxicology, septic screen
• Ascertain if: PMH; medications; drug abuse; intercurrent illness; history of epilepsy; PNES.
• Consider videoing if ?PNES.
• Establish whether any treatments have been given prior to arrival in hospital
• If suspicion of alcohol excess or malnourishment, give Pabrinex
• Replace glucose if hypoglycemic
• Prepare a benzodiazepine for administration
Early status epilepticus (5-20 minutes)
• Monitor vital signs
• Institute cardiac monitoring
• Contact ICU if no response to first benzodiazepine
• Give a benzodiazepine (see figure 2)
• If no response after 5 minutes, give a second dose of benzodiazepine.
Established status epilepticus (20-40 mins)
• ICU review
• Chest X-ray
• Consider CT head if first seizure, new focal neurology, head injury
• Consider intubation
Give 2nd line AED IV (see figure 3):
• Phenytoin/fosphenytoin
• Sodium valproate
• Levetiracetam
Refractory status epilepticus (>30 mins)
• Intubate and admit to ICU
• Consider EEG
• Anaesthetic agents (eg. Thiopental, propofol, midazolam)

Fig. 1. Flow diagram for general and pharmacological management of convulsive status epilepticus.
FBC – full blood count; U&E – urea and electrolytes; LFT – liver function tests; CRP – C-reactive protein; Mg – magnesium; TFT – thyroid function tests. PMH – past medical history; AED – anti-epileptic drug; PNES – psychogenic non-epileptic seizure

hospital, is also likely to reduce healthcare costs [5]. Although no individual study can definitively prove cause and effect, a clear message is coming through.

3. General management and diagnostic issues

3.1. First aid and general medical considerations

Key management considerations are summarized in Fig. 1. Given the importance of speed it is important to check the time at seizure onset and estimate duration if receiving handover from bystanders or emergency medical services. Guidelines then advocate an 'ABC' approach, necessitating that the airway be secured in the first instance. During convulsions, it is muscle (including laryngeal) spasm that restricts air entry, so this is best achieved by stopping the seizures. Any attempt to insert an oral airway may cause injury in an actively seizing patient. Airway manoeuvres such as head tilt and jaw thrust can be helpful post-ictally, though many patients will require a nasopharyngeal airway with oxygen therapy to maintain adequate saturations. Vital signs should be monitored and cardiac monitoring instituted. Cardiac complications are not infrequent [3], and some of the drugs used, particularly phenytoin can also have cardiac side effects. Intravenous access should be established early, alongside checking blood glucose, with further blood samples sent (see Fig. 1) to investigate the potential cause and consequences of SE. Investigations are also covered in the preceding article in this supplement. If there are concerns regarding alcohol excess or poor nutrition, 250 mg IV thiamine should be given followed by 50 mL of 50% glucose IV if the patient is hypoglycaemic.

The above management should all be instituted as rapidly as possible, ideally within the first few minutes of arrival at hospital or prehospital where possible. For this reason, amongst others, it is also important to seek help early so that these steps can be carried out in parallel by different members of the multi-disciplinary team.

3.2. Are you sure it's epileptic status epilepticus?

Whilst not the topic of this article, the importance of considering the

Table 2
Clinical Features helpful in distinguishing epileptic from dissociative seizures [14,15].

Favour Dissociative Seizures	Not useful discriminators
Long (> 5 minutes) duration of individual events	Tongue biting (except possibly lateral)
Fluctuating course (waxing and waning)	Incontinence
Asynchronous rhythmic movements[a]	Gradual onset
Pelvic thrusting[a]	Non-stereotyped
Side to side head/body movements during a convulsion	Flailing/thrashing movements
Closed eyes	Opisthotonus
Ictal Crying	Associated Injuries[21]
Recall of items during event[b]	

[a] Can be seen in frontal lobe focal seizures. [b]Patients often report being able to hear what is going on around them but not being able to respond. Features favouring epileptic seizures include prolonged post-event confusion and stertorous breathing. Table reproduced with permission from [16].

possibility that persistent or recurrent convulsions might be dissociative (psychogenic non-epileptic seizures) rather than epileptic status epilepticus must not be overlooked. Frequent admissions should be considered a red flag, and a reported diagnosis of epilepsy is not uncommon – either due to prior misdiagnosis, or a dual diagnosis. There is no fool-proof clinical marker, but key features which can help distinguish dissociative from epileptic seizures are summarized in Table 2. Emergency physicians may be insufficiently experienced to confidently distinguish the two. Perhaps inevitably, the team may initially manage as for epileptic status epilepticus. However, if there is any diagnostic doubt at all, early video recording of the events in parallel with treatment can be extremely helpful to the specialist later called in to advise on longer term management. As with any form of imaging, whilst there is often concern about the sensitive nature of a video, and inability to take consent in this context, video should be considered a critical diagnostic test, and is justifiable as a best interests intervention to inform management [59]. EEG is rarely available in the emergency setting, but expert review of "home" video has been shown to be over 95% sensitive and specific [12] for the diagnosis of dissociative seizures. The use of personal devices for recording is also not precluded, providing appropriate steps to protect the data are applied. These include using a password protected device, disabled cloud syncing, and transferring the files to the hospital records system as soon as possible using encrypted systems. Patient consent can be sought on recovery, and the data deleted if not given, with full documentation of decision making and actions throughout this process. Especially considering the risks of inappropriate sedation and intensive care admission in this population, including iatrogenic death [13] and the impact of the correct diagnosis on management, this is surely reasonable.

4. Initial pharmacological treatment of convulsive status epilepticus

First line medical treatments for status epilepticus may be instituted in the community, by emergency medical services or in the hospital. Whilst the focus of this review is on hospital treatment, much of the evidence around initial treatment of convulsive SE comes from prehospital studies. The most appropriate drug route will vary depending on the setting and consequent practicalities and safety considerations. There have been dozens of adult and paediatric studies published on the efficacy and safety of benzodiazepines via various routes and several recent systematic reviews/meta-analyses. Methodological heterogeneity, including in study populations, trial design, primary outcome definitions and approaches to analysis contribute to some differences in conclusions between individual studies. Nevertheless, there is broad consensus to guide first line treatment, as summarized in Fig. 2. The majority of trials have focused on the use of benzodiazepines, specifically lorazepam, diazepam, midazolam and clonazepam. The main questions addressed relate to which particular benzodiazepine is preferable in terms of speed of onset and duration of action, safety, and impact of route of administration.

4.1. Intravenous benzodiazepines

For all agents, there is consensus that if intravenous (IV) access is already in place, IV administration of benzodiazepines leads to shorter time to seizure termination [17]. IV lorazepam has been found to be at least as effective as IV diazepam in all meta-analyses performed [18–20] whether in adult or paediatric populations. A potential advantage of lorazepam is its longer duration of action compared with diazepam. Some earlier studies report fewer patients needing repeat doses or additional AEDs to terminate SE, but there is not strong evidence to support superiority of lorazepam. IV midazolam has also been shown to be as effective as both IV lorazepam and IV diazepam, although in practice this has rarely been used as initial treatment [18]. IV clonazepam, which has a long half-life and rapid onset of action, is also widely used across parts of Europe, although the evidence was until recently based only on uncontrolled case series [21]. A randomized prehospital trial in in 2016 [22] evaluated the use of IV clonazepam plus either levetiracetam or placebo for the initial treatment of SE. Seizures were stopped within 15 minutes of Clonazepam plus placebo in 84% of patients, so it is clearly effective but has not been compared with other IV benzodiazepines in a clinical trial setting.

4.2. Non-intravenous benzodiazepines

In or out of hospital, unless IV access is already in situ, non-IV routes may be preferable as faster administration can offset the slightly slower onset of action, meaning shorter time to seizure cessation overall. This was demonstrated most clearly in the RAMPART trial, which though set up as a non-inferiority (10% difference) study demonstrated that intramuscular (IM) midazolam is superior to IV lorazepam in the prehospital setting [23]. 893 adults were randomized to either drug. 73% of those receiving IM midazolam (10 mg in adults, 5 mg in children) were seizure-free when arriving in the emergency department vs 63% receiving IV lorazepam (4 mg in adults, 2 mg in children), with the main advantage being shorter time to treatment initiation. Intranasal midazolam and buccal midazolam are also effective non-intravenous options for initial management of SE [24], however the existing comparative evidence for these is less strong than for IM midazolam [18]. Arya et al evaluated the efficacy of various non-venous medications for acute convulsive seizures, incorporating data from 16 trials [25]. They concluded that IM and intranasal midazolam exhibit the best efficacy data for treatment of SE in the absence of IV access. Rectal diazepam is also well-established and relatively cheap, effective option. However, non-IV forms of midazolam are not only associated with shorter time to seizure termination but are also more practical and often more socially acceptable to patients and care-givers than rectal medications [24,26].

There are a number of studies looking at non-IV lorazepam, including intranasal, sublingual or rectal administration [25]. Some studies suggest similar efficacy, but with less consistent data and smaller numbers thus far, such that none are yet recommended as first line options [17].

Overall, the evidence supports use of a non-IV benzodiazepine, preferably Midazolam where IV access is not already present, with choice of agent overall being less important than speed of administration, particularly once IV access is established.

4.3. Non-benzodiazepines as initial therapy for SE

A few studies have looked at alternatives to benzodiazepines as initial treatment in SE. Drugs evaluated include phenobarbital, levetiracetam, sodium valproate and phenytoin. One of the earliest, large

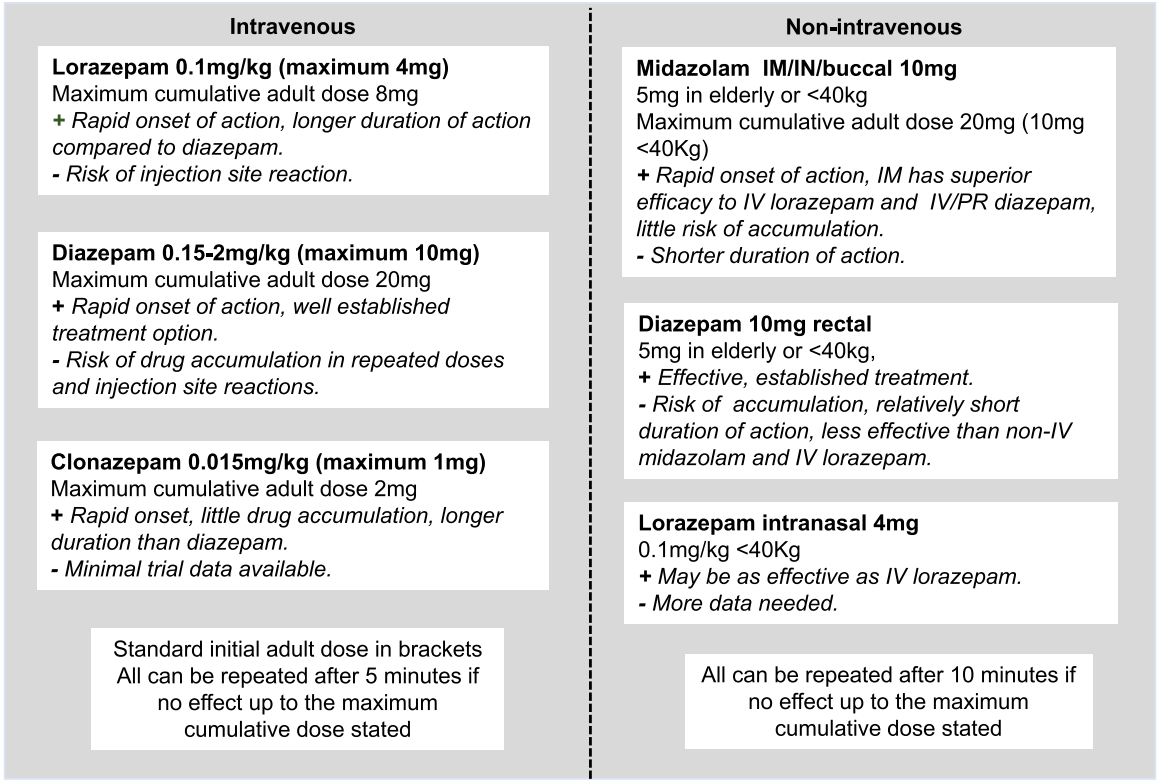
Intravenous
Lorazepam 0.1mg/kg (maximum 4mg)
Maximum cumulative adult dose 8mg
+ Rapid onset of action, longer duration of action compared to diazepam.
- Risk of injection site reaction.
Diazepam 0.15-2mg/kg (maximum 10mg)
Maximum cumulative adult dose 20mg
+ Rapid onset of action, well established treatment option.
- Risk of drug accumulation in repeated doses and injection site reactions.
Clonazepam 0.015mg/kg (maximum 1mg)
Maximum cumulative adult dose 2mg
+ Rapid onset, little drug accumulation, longer duration than diazepam.
- Minimal trial data available.
Standard initial adult dose in brackets
All can be repeated after 5 minutes if no effect up to the maximum cumulative dose stated
Non-intravenous
Midazolam IM/IN/buccal 10mg
5mg in elderly or <40kg
Maximum cumulative adult dose 20mg (10mg <40Kg)
+ Rapid onset of action, IM has superior efficacy to IV lorazepam and IV/PR diazepam, little risk of accumulation.
- Shorter duration of action.
Diazepam 10mg rectal
5mg in elderly or <40kg,
+ Effective, established treatment.
- Risk of accumulation, relatively short duration of action, less effective than non-IV midazolam and IV lorazepam.
Lorazepam intranasal 4mg
0.1mg/kg <40Kg
+ May be as effective as IV lorazepam.
- More data needed.
All can be repeated after 10 minutes if no effect up to the maximum cumulative dose stated

Fig. 2. Benzodiazepines for initial treatment of status epilepticus.
All benzodiazepines can cause respiratory depression, sedation and hypotension at higher doses and in susceptible patients. + relative benefits and – disadvantages

randomized control trials in SE [27] demonstrated that IV lorazepam 0.1 mg/kg has similar efficacy to both IV phenobarbital 18 mg/kg and to combined IV diazepam 0.15 mg/kg with phenytoin 18 mg/kg. IV lorazepam was significantly more effective than phenytoin alone. Phenobarbital may therefore be an effective option for initial treatment, however in practice this is rarely used due to concerns about long term side effects and potential respiratory depression. Evidence from this trial suggests that phenytoin alone should not be recommended as a first line treatment.

There are no trials comparing sodium valproate alone with a benzodiazepine for initial treatment of SE. Three trials have been undertaken comparing sodium valproate with phenytoin, either alone [28,29], or in combination with diazepam [30] as first line treatment. All are small and underpowered. One [27] suggested valproate was more efficacious than phenytoin, and one suggested phenytoin had more adverse events [29]. Levetiracetam has also been evaluated as an initial treatment of SE. In an open pilot study IV lorazepam (0.1 mg/kg) controlled seizures in 75.6% of patients, compared to 76.3% given IV levetiracetam 20 mg/kg as initial treatment of convulsive status [31]. Seizure freedom at 24 hours was also comparable between the two groups. Lorazepam was associated with significantly higher need for intubation and ventilation. Rates of hypotension were also higher with lorazepam administration, though not significantly so. A more recent double-blinded randomized trial analyzed efficacy of levetiracetam with clonazepam vs clonazepam with placebo [22]. In the modified intention to treat analysis, seizures were terminated by 15 minutes in 87% of 68 patients treated with clonazepam and placebo compared with 74% of the 68 pre-hospital patients receiving levetiracetam and clonazepam. There was no significant difference between the two groups.

Thus, as we will go onto discuss, although sodium valproate and levetiracetam may be safe and effective, there is not enough evidence to recommend them as first line treatments of SE, unless and until such time as any clear advantages compared to benzodiazepines are demonstrated which is not yet the case. That both require IV access is also a significant disadvantage as first line treatment.

5. Second line antiepileptics for established SE

Although there is consensus and good evidence to support benzodiazepines as the drug of choice for initial treatment of SE, until recently there was much less evidence to help choose which AED should be used in established SE, when benzodiazepines have failed.

Choice of AED has been largely dictated by availability of IV formulations given the clinical context. Historically only phenytoin or phenobarbitone were used and remain (including fosphenytoin) the only currently licensed medications in established SE. Phenytoin in combination with a benzodiazepine, and phenobarbitone are both effective as evidenced by the Trieman study cited in 4.3 [27]. However, there is accumulating data suggesting clinical equipoise between phenytoin and newer AEDs such as sodium valproate or levetiracetam. Each has specific potential advantages and disadvantages depending on the clinical context as summarized in Fig. 3, with a considerable body supporting utility in practice. However, prior to 2019 much of the published data was retrospective, and any clinical trials in established SE had substantial methodological limitations, making it difficult to draw firm conclusions. The best comparative data was from meta-analysis [32]. This estimated the efficacy of levetiracetam to be 68.5% (95% CI: 56.2%–78.7%), phenobarbital 73.6% (95% CI: 58.3%–84.8%), phenytoin 50.2% (95% CI: 34.2%–66.1%) and valproate 75.7% (95% CI: 63.7%–84.8%). However, the quality of evidence is such that this can't be considered definitive. Most studies had been underpowered; inclusion criteria were variable (many including a mix of convulsive, non-convulsive and focal SE); definitions of treatment efficacy also varied; some included a high proportion with acute symptomatic epilepsy and consequent better outcomes; and most of the existing trials had been open label.

Drug	Dose; Rate (Maximum)	May be preferable	Contraindications & Cautions
(fos)Phenytoin	20mg/kg; 50mg/min (2000mg)	• Already taking phenytoin, suspected poor adherence • Alternatives contra-indicated or previously ineffective	• Significant hypotension • Bradycardia, heart block • Porphyria • Generalized epilepsy • Overdose of recreational drugs or antidepressants
Valproate	30mg/kg; 10mg/kg/min (3000mg)	• Already taking valproate, suspected poor adherence • Generalized epilepsy • Comorbid migraine, mood disorder • Alternatives contra-indicated or previously ineffective	• Women of childbearing age[1] • Pre-existing liver disease or pancreatitis • Known metabolic disorder predisposing to hepatotoxicity • Caution in acute stroke or brain injury (risk of thrombocytopenia)
Levetiracetam	60mg/kg; 6mg/kg/min (4500mg)	• Already taking levetiracetam, suspected poor adherence • Need for minimal drug interactions • Alternatives contra-indicated or previously ineffective	May not be best choice in: • acute or prior brain injury[2] • known mood/behaviour disorder (may exacerbate) • Reduce dose in renal impairment

Fig. 3. Effective treatment options for established status epilepticus.
(fos)Phenytoin doses shown are for phenytoin, or phenytoin equivalents for fosphenytoin. [1]Relative contraindication. Status epilepticus also poses a risk to the woman, and her unborn child. In an emergency situation, especially in a generalized epilepsy or where Levetiracetam is contraindicated, seizure control should take priority. [2] Relative contraindication. This patient group anyway at high risk of fatigue and mood disorders, so may be more vulnerable to these adverse effects on levetiracetam.

5.1. Phenytoin and fosphenytoin

Phenytoin is one of the oldest drugs used in established SE. As summarized in section 6, current efficacy data suggest a potentially lower efficacy than alternatives. Non-linear kinetics can result in sub-therapeutic drug levels, despite recommended dosing at 18-20 mg/kg. To what extent this might impact on reported efficacy is uncertain, with levels often not evaluated in trials, but in practice this is still a relevant consideration. Commonly occurring side effects include thrombophlebitis, cardiac arrhythmias (occassionally fatal) and hypotension, particularly in more elderly patients [34]. Of particular note, from reports to the UK National Patient Safety Agency over 5 years [60], phenytion was the only drug in which loading dose errors were associated with fatalities. It also has the disadvantage of exacerbating seizures in some patients with idiopathic generalised epilepsies such as juvenile myoclonic epilepsy.

Its prodrug fosphenytoin has a number of comparative advantages [35], including fewer infusion site reactions, and availability of an intramuscular formulation allowing for potentially quicker and easier administration. It is considerably more expensive than phenytoin however, and cost-efficacy analyses have yielded contradictory recommendations regarding its use [36,37]. Furthermore, in contrast to valproate and levetiracetam, phenytoin is not currently recommended as an early maintenance treatment option for epilepsy so loading with another agent may be preferable when continuation treatment is considered. Thus whilst phenytoin has traditionally been the drug of choice in SE and undoubtedly can be effective, there is a growing body of evidence to suggest that other antiepileptics may be preferable on efficacy, safety and practical grounds.

5.2. Sodium valproate

Sodium valproate is also a well-established first generation anti-epileptic drug, though it was not available as an IV formulation until 1993. Doses ranging between 25–40 mg/kg have been shown to be both safe and effective in SE [38]. Overall valproate is well tolerated with a low frequency of adverse events (< 10%). In some patients it can cause dizziness, mild hypotension and mild thrombocytopenia. In light of the latter, it may be best avoided in acute stroke. It should also be avoided in patients with known liver disease and/or metabolic encephalopathy. Sodium valproate can be hepatotoxic with the potential to cause an encephalopathy, either with or without raised ammonia. It is also best avoided in patients aged less than 2 years old, particularly if as part of polytherapy, due to increased potential hepatic dysfunction and as yet undiagnosed metabolic problems [39].

Several open label trials have been published comparing sodium valproate with phenytoin for treatment of benzodiazepine-resistant SE [28,29,40]. Although meta-analysis demonstrated only a non-significant trend towards valproate being more efficacious [32], but with fewer adverse events, especially less hypotension, compared to phenytoin. For patients who are already taking oral sodium valproate for epilepsy, given that poor adherence is a common provoker of SE, it could be considered the drug of choice. Similarly, it may be preferable in patients with contraindications to phenytoin such as brady-arrhythmias or in those with genetic/idiopathic generalised epilepsy where sodium channel blockers can be aggravating. As such, it is already incorporated in some International SE guidelines [17] as an effective alternative to phenytoin.

5.3. Levetiracetam

Levetiracetam is a 2nd generation well-tolerated anti-epileptic drug which has been available as an IV preparation since 2006. Again, meta-analysis [32] suggests at least similar efficacy to valproate and phenytoin, typically with reported loading doses of at least 20–30 mg/kg, totalling between 1–3 g. A subsequent small open label study adds to this evidence, with seizure cessation achieved in 78.6% of 30 patients [41]. Adverse events occur in < 10%. They tend to be mild and

transient, but can include drowsiness, thrombocytopenia, agitation and post-ictal psychosis [42]. Levetiracetam is possibly thus best avoided in patients with known brain injury or mood disorders as it may exacerbate behavioural disturbance. The drug is renally excreted, and so dose adjustments are also recommended in renally impaired patients. Levetiracetam has been shown to be safe when given at much higher doses (40–60 mg/kg), with the potential to be more effective than existing studies have demonstrated. Based on current evidence, international guidelines recommend levetiracetam as an option in established SE, with doses of 60 mg/kg up to a ceiling of 4500 mg [17], despite that, as with valproate, it is not yet licensed for this indication [43,44,61].

5.4. Recent randomised controlled trials

Two phase IV, well powered open randomized controlled trials reported during 2019 [44,45], with results from the pivotal USA double blinded ESETT in adults and children [46,47] expected imminently. All enrolled individuals with ongoing convulsive SE despite minimum adequate benzodiazepines, and relied on a clinical decision that convulsive SE had ended without other anticonvulsant medication as the primary outcome. Other key methodological differences and the primary outcome results where available are summarised in Table 3. Thus far no significant differences in efficacy have been found. The incidence of key safety endpoints such as life threatening hypotension or arrhythmia was very low, with expected rates of endotracheal intubation, again with no significant differences between the agents. There are methodological pros and cons with each of the studies, too numerous to detail here. However, taking into account the broader safety profiles of each of the agents given in the acute situation together with the practicalities of administration suggests levetiracetam at least may be preferable to phenytoin in most cases, pending the release from ESETT. Both levetiracetam and valproate can for example be given in less than 5–10 minutes even in a large adult, have fewer drug interactions in a patient group who often have comorbidities or complications needing other treatments, and are commonly used maintenance treatments thereafter.

5.5. Phenobarbitone

Phenobarbitone is also an effective and established drug for treatment of both initial and established SE, with efficacy and safety demonstrated in older [27] and more recent studies, [44]. It was first used as an AED in 1912, and has subsequently been developed in formulations for rectal, IV and subcutaneous administration. It is cheap with good global availability, though has fallen out of fashion in developed countries where newer agents are more widely available. Meta-analysis supports comparative efficacy with levetiracetam [32] and sodium valproate [32,45]. A more recently published non-blinded Chinese RCT randomised 73 patients to receive either 30 mg/kg sodium valproate or 20 mg/kg phenobarbital. Valproate had an unusually low efficacy (44.4%), significantly lower than phenobarbital (81.1%) in this study, raising the possibility of ethnic influences on response, though methodological and study population differences may also account for this [46]. The main influence limiting utility of phenobarbitone where alternatives are available however is the higher frequency of adverse events [47] including sedation, hypotension and respiratory depression.

5.6. Lacosamide and other new AEDs

Lacosamide has been available as an IV preparation since 2008. It is licensed as an adjunctive treatment in patients with focal seizures with or without secondary generalisation, and increasingly used in SE, summarized in a recent systematic review [48]. The most common doses used in SE include a loading dose of 400 mg with a subsequent maintenance dose of 400 mg per day. The most appropriate dose in mg/kg, as would be the more usual approach in SE, has yet to be agreed. Some have suggested 6 mg/kg with a ceiling of 600 mg, though outside of SE, doses up to 9 mg/kg are typically required to achieve therapeutic levels [49]. Side effects include dizziness and rash. Bradycardia and hypotension have also rarely been reported, but overall it is a well-tolerated at these doses, with a low risk of drug interactions.

The majority of studies evaluating lacosamide in SE have been retrospective, descriptive studies with considerable heterogeneity in type of SE (including focal and non-convulsive SE). There was also much variation in the stage that lacosamide was added, even within individual studies. Some were in established status, but most were in either refractory or super-refractory SE. A meta-analysis of these heterogenous studies found lacosamide to be 57% effective overall, and in a post hoc subgroup analysis, it was found to be 92% effective in focal motor SE. Meta-analysis of studies in established convulsive SE [32] found from 13 papers evaluating lacosamide, only 4 patients who were treated with lacosamide second line after benzodiazepine failure, limiting conclusions.

There is clearly considerable interest however, with two more recently published studies: In an open trial from India [50] 66 patients were randomised to valproate or lacosamide after initial benzodiazepine treatment had failed, with no significant differences in efficacy though as with all the studies from this group thus far it was underpowered, and had a high proportion of acute symptomatic seizures. A more recent randomised non-inferiority prospective study in 2018 compared lacosamide with fosphenytoin in 74 patients with non-convulsive status [51] and similarly found no significant differences in efficacy or safety, though there was significant heterogeneity in the number and choice of other AEDs which had already been employed.

Overall there is not currently enough evidence to recommend use of lacosamide in established SE, though arguably also not enough to discount it as an option other than perhaps in idiopathic generalized epilepsies, where like phenytoin is may be less effective or even aggravate seizures [52]. A number of case reports and case series have been published on other new AEDs in SE, including perampanel [53], brivaracetam [54] and rufinamide [55]. However, unsurprisingly these are typically used in cases of refractory and super-refractory SE, and it

Table 3
Phase IV Randomized trials of newer agents compared to Phenytoin reporting in 2019.

Trial [ref]	Treatment arms (dose mg/kg, infusion minutes)	Age (n)	Primary outcome	
			Definition	Results* PHT, LEV, VPA
EcLiPSE [44]	PHT (20,20) LEV (40,5)	6 months < 18 years (286)	Time from randomisation to clinical cessation of convulsive status	35 minutes, 45 minutes, NA
ConSEPT [45]	PHT (20,20) LEV (40,5)	3 months – 16 years (233)	Clinical cessation seizures 5 minutes after infusion completed	60%, 50%, NA
ESETT	fosPHT (20,10) LEV (60,10) VPA (40,10)	1 – 94 years (400)	Absence of clinically evident seizures and improving consciousness 1 hour after infusion	Imminent

PHT = phenytoin; LEV = levetiracetam; VPA = valproate. N = total number recruits, equally randomised between treatment arms; *none significant.

is likely to be many years if ever before there is sufficient evidence to consider them earlier in the treatment pathway.

6. Other types of SE

A comprehensive review of treatment for other types of SE is beyond the scope of this article. Absence status, and myoclonic status in the context of an idiopathic generalized epilepsy should be treated, though at least for Absence SE there is less urgency, and ideally with confirmation using EEG. As for convulsive SE, benzodiazepines are first line, followed by either valproate or levetiracetam. In older patients, absence status may present de novo, often precipitated by benzodiazepine withdrawal and will usefully respond to a small dose (e.g.1 mg of Lorazepam), repeated if needed. Initial steps for Focal SE follow the same algorithm as for SE, but usually with sequential trials of alternative intravenous AEDs sometimes over days or longer before resorting to sedation. Focal Motor SE (Epilepsia partialis contrinua) is often drug resistant, and whilst irritating and disabling, rarely dangerous, meaning the risks of sedation may not be justifiable. For non-convulsive SE, EEG confirmation will usually be required, but appropriate timing and aggressiveness of treatment is controversial, and informed by the frailty, cause and potential outcome for the individual [56]. For patients in NCSE without coma, most would try to avoid ICU if possible. For those with coma, ICU management will often be inevitable, and ongoing management is covered by other articles in this issue.

7. Future potential areas for research

Given the results of the two open trials already published in 2019 [43,44], and pending the blinded ESETT results [33,61], whether there will be an appetite for further large adequately powered studies in established SE remains to be seen. There is emerging interest in the potential for rapid EEG in the emergency setting, of likely benefit in identifying dissociative non-epileptic seizures (clear alpha rhythm in an unresponsive patient, between convulsive movements excludes epileptic SE as the cause). This could also potentially detect ongoing subtle status in those patients who fail to wake, and prompt administration of additional AEDs, though whether this would influence outcome remains uncertain.

One ongoing concern not yet resolved is how best to support the delivery of evidence-based treatment in routine clinical practice. Despite well established guidelines, numerous studies in multiple settings [57], includign within the ESETT study [62] have demonstrated a culture of initial underdosing and delays in the management of convulsive SE, as well as cumulative overdosing with benzodiazepines negatively impacting on patient outcomes. One root cause analysis study exploring this on a paediatric unit [58] identified inconsistency and delays in physician decision making as a key determinant, improved by use of electronic timed “power plans”. Identifying barriers and quality improvement work should be a priority.

8. Conclusions

Speed is of the essence in treatment of SE. Based on current evidence, IV lorazepam or diazepam, or non-IV midazolam remain first choice for initial treatment of SE. Although phenytoin and phenobarbital have been used traditionally, levetiracetam and potentially sodium valproate may be preferable in the majority of patients on current evidence.

Acknowledgements

The ESETT on which Prof Cock is an investigator was supported by awards U01NS088034, U01NS088023, U01NS056975, U01NS059041, U01NS073476 from the National Institute of Neurological Disorders and Stroke (NINDS).

References

[1] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515–23.
[2] Neligan A, Shorvon SD. Prognostic factors, morbidity and mortality in tonic-clonic status epilepticus: a review. Epilepsy Res 2011;93:1–10.
[3] Sutter R, Dittrich T, Semmlack S, Ruegg S, Marsch S, Kaplan PW. Acute systemic complications of convulsive status epilepticus-a systematic review. Crit Care Med 2018;46:138–45.
[4] Gainza-Lein M, Fernandez IS, Jackson M, Abend NS, Arya R, Brenton JN, et al. Association of time to treatment with short-term outcomes for pediatric patients with refractory convulsive status epilepticus. JAMA Neurol 2018;75:410–8.
[5] Santamarina E, Parejo B, Abraira L, Gutiérrez-Viedma Á, Alpuente A, Abarrategui B, et al. Cost of status epilepticus (SE): effects of delayed treatment and SE duration. Epilepsy Behav 2018;89:8–14.
[6] Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. Epilepsia 1994;35:27–34.
[7] Eriksson KJ, Koivikko MJ. Status epilepticus in children: aetiology, treatment, and outcome. Dev Med Child Neurol 1997;39:652–8.
[8] Sagduyu A, Tarlaci S, Sirin H. Generalized tonic-clonic status epilepticus: causes, treatment, complications and predictors of case fatality. J Neurol 1998;245:640–6.
[9] Gulati S, Kalra V, Sridhar MR. Status epilepticus in Indian children in a tertiary care center. Indian J Pediatr 2005;72:105–8.
[10] Drislane FW, Blum AS, Lopez MR, Gautam S, Schomer DL. Duration of refractory status epilepticus and outcome: loss of prognostic utility after several hours. Epilepsia 2009;50:1566–71.
[11] Power KN, Gramstad A, Gilhus NE, Engelsen BA. Prognostic factors of status epilepticus in adults. Epileptic Disord 2016;18:297–304.
[12] Ramanujam B, Dash D, Tripathi M. Can home videos made on smartphones complement video-EEG in diagnosing psychogenic nonepileptic seizures? Seizure 2018;62:95–8.
[13] Reuber M, Baker GA, Gill R, Smith DF, Chadwick DW. Failure to recognize psychogenic nonepileptic seizures may cause death. Neurology 2004;62:834–5.
[14] LaFrance WC, Baker GA, Duncan R, Goldstein LH, Reuber M. Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: a staged approach A report from the International League Against Epilepsy Nonepileptic Seizures Task Force. Epilepsia 2013;54:2005–18.
[15] Avbersek A, Sisodiya S. Does the primary literature provide support for clinical signs used to distinguish psychogenic nonepileptic seizures from epileptic seizures? J Neurol Neurosurg Psychiatr 2010;81:719–25.
[16] Cock HR, Edwards MJ. Functional neurological disorders: acute presentations and management. Clin Med 2018;18:414–7.
[17] Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the american epilepsy society. Epilepsy Curr 2016;16:48–61.
[18] McTague A, Martland T, Appleton R. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews. 2018.
[19] Wu W, Zhang LQ, Xue R. Lorazepam or diazepam for convulsive status epilepticus: a meta-analysis. J Clin Neurosci 2016;29:133–8.
[20] Brigo F, Bragazzi NL, Bacigaluppi S, Nardone R, Trinka E. Is intravenous lorazepam really more effective and safe than intravenous diazepam as first-line treatment for convulsive status epilepticus? A systematic review with meta-analysis of randomized controlled trials. Epilepsy Behav 2016;64:29–36.
[21] Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, et al. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: a multicenter comparison. Epilepsia 2015;56:1275–85.
[22] Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47–55.
[23] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366:591–600.
[24] Brigo F, Nardone R, Tezzon F, Trinka E. Nonintravenous midazolam versus intravenous or rectal diazepam for the treatment of early status epilepticus: a systematic review with meta-analysis. Epilepsy Behav 2015;49:325–36.
[25] Arya R, Kothari H, Zhang Z, Han B, Horn PS, Glauser TA. Efficacy of nonvenous medications for acute convulsive seizures: a network meta-analysis. Neurology 2015;85:1859–68.
[26] Haut SR, Seinfeld S, Pellock J. Benzodiazepine use in seizure emergencies: a systematic review. Epilepsy Behav 2016;63:109–17.
[27] Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, Handforth A, Faught E, Calabrese VP, Uthman BM, Ramsay RE, Mamdani MB. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339:792–8.
[28] Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology 2006;67:340–2.
[29] Gilad R, Izkovitz N, Dabby R, Rapoport A, Sadeh M, Weller B. Treatment of status epilepticus and acute repetitive seizures with i.v. Valproic acid vs phenytoin. Acta Neurol Scand 2008;118:296–300.

[30] Rai A, Aggarwal A, Mittal H, Sharma S. Comparative efficacy and safety of intravenous valproate and phenytoin in children. Pediatr Neurol 2011;45:300–4.
[31] Misra UK, Kalita J, Maurya PK. Levetiracetam versus lorazepam in status epilepticus: a randomized, open labeled pilot study. J Neurol 2012;259:645–8.
[32] Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23:167–74.
[33] Bleck T, Cock H, Chamberlain J, Cloyd J, Connor J, Elm J, et al. The established status epilepticus trial 2013. Epilepsia 2013;54:89–92.
[34] Rohracher A, Reiter DP, Brigo F, Kalss G, Thomschewski A, Novak H, et al. Status epilepticus in the elderly-A retrospective study on 120 patients. Epilepsy Res 2016;127:317–23.
[35] Biton V, Rogin JB, Krauss G, Abou-Khalil B, Rocha JF, Moreira J, et al. Adjunctive eslicarbazepine acetate: a pooled analysis of three phase III trials. Epilepsy Behav 2017;72:127–34.
[36] Rudis MI, Touchette DR, Swadron SP, Chiu AP, Orlinsky M. Cost-effectiveness of oral phenytoin, intravenous phenytoin, and intravenous fosphenytoin in the emergency department. Ann Emerg Med 2004;43:386–97.
[37] Armstrong EP, Sauer KA, Downey MJ. Phenytoin and fosphenytoin: a model of cost and clinical outcomes. Pharmacotherapy 1999;19:844–53.
[38] Trinka E, Hoefler J, Zerbs A, Brigo F. Efficacy and safety of intravenous valproate for status epilepticus: a systematic review. CNS Drugs 2014;28:623–39.
[39] Bryant AE, Dreifuss FE. Valproic acid hepatic fatalities .3. US experience since 1986. Neurology 1996;46:465–9.
[40] Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure 2007;16:527–32.
[41] Atmaca MM, Orhan EK, Bebek N, Gurses C. Intravenous levetiracetam treatment in status epilepticus: a prospective study. Epilepsy Res 2015;114:13–22.
[42] Trinka E, Dobesberger J, Brossner G, Unterberger I, Walser G, Ehling R, et al. The use of intravenous levetiracetam in status epilepticus and acute seizure emergencies. Epilepsia 2008;49. 459-459.
[43] Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. The Lancet 2019;393(10186):2125–34. https://doi.org/10.1016/S0140-6736(19)30724-X.
[44] Dalziel SR, Borland ML, Furyk J, Bonish M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. The Lancet 2019;393(10186):2135–45. https://doi.org/10.1016/S0140-6736(19)30722-6.
[45] Brigo F, Igwe SC, Nardone R, Tezzon F, Bongiovanni LG, Trinka E. A common reference-based indirect comparison meta-analysis of intravenous valproate versus intravenous phenobarbitone for convulsive status epilepticus. Epileptic Disord 2013;15:314–23.
[46] Su YY, Liu G, Tian F, Ren GP, Jiang MD, Chun B, et al. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults: a prospective randomized controlled trial in China. CNS Drugs 2016;30:1201–7.
[47] Brigo F, Bragazzi N, Nardone R, Trinka E. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy Behav 2016;64:110–5.
[48] Strzelczyk A, Zollner JP, Willems LM, Jost J, Paule E, Schubert-Bast S, et al. Lacosamide in status epilepticus: systematic review of current evidence. Epilepsia 2017;58:933–50.
[49] Santamarina E, Gonzalez-Cuevas M, Toledo M, Jimenez M, Becerra JL, Quilez A, et al. Intravenous lacosamide (LCM) in status epilepticus (SE): weight-adjusted dose and efficacy. Epilepsy Behav 2018;84:93–8.
[50] Misra UK, Dubey D, Kalita J. Comparison of lacosamide versus sodium valproate in status epilepticus: a pilot study. Epilepsy Behav 2017;76:110–3.
[51] Husain AM, Lee JW, Kolls BJ, Hirsch LJ, Halford JJ, Gupta PK, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol 2018;83:1174–85.
[52] Wechsler RT, Yates SL, Messenheimer J, Leroy R, Beller C, Doty P. Lacosamide for uncontrolled primary generalized tonic-clonic seizures: an open-label pilot study with 59-week extension. Epilepsy Res 2017;130:13–20.
[53] Beuchat I, Novy J, Rossetti AO. Newer antiepileptic drugs in status epilepticus: prescription trends and outcomes in comparison with traditional agents. CNS Drugs 2017;31:327–34.
[54] Kalss G, Rohracher A, Leitinger M, Pilz G, Novak HF, Neuray C, Kreidenhuber R, Hofler J, Kuchukhidze G, Trinka E. Brivaracetam in established status epilepticus: the Salzburg experience. Epilepsia 2017;58. S197-S197.
[55] Thompson AGB, Cock HR. Successful treatment of super-refractory tonic status epilepticus with rufinamide: first clinical report. Seizure-European Journal of Epilepsy 2016;39:1–4.
[56] van Rijckevorsel K, Boon P, Hauman H, Legros B, Ossemann M, Sadzot B, et al. Standards of care for non-convulsive status epilepticus: belgian consensus recommendations. Acta Neurol Belg 2006;106:117–24.
[57] Uppal P, Cardamone M, Lawson JA. Outcomes of deviation from treatment guidelines in status epilepticus: a systematic review. Seizure-Eur J Epilepsy 2018;58:147–53.
[58] Xie Y, Morgan R, Schiff L, Hannah D, Wheless J. A computerized standard protocol order entry for pediatric inpatient acute seizure emergencies reduces time to treatment. J Child Neurol 2014;29:162–6.
[59] General Medical Council: Making and using visual and audio recordings of patients. 2011.
[60] National Patient Safety Agency, Rapid Response Report NSPA/2010/RRR018. Preventing Fatalities form medication loading doses. 2010.
[61] Cock HR, Coles LD, Elm JJ, Silbergleit R, Chamberlain JM, Cloyd J, et al. Lessons from the Established Status Epilepticus Treatment Trial. Epilepsy and Behaviour 2019. https://doi.org/10.1016/j.yebeh.2019.04.049. In press.
[62] Sathe AG, Tilman H, Coles LD, Elm JJ, Silbergleit R, Chamberlain J, et al. Underdosing of Benzodiazepines in Patients With Status Epilepticus Enrolled in Established Status Epilepticus Treatment Trial. Academic Emergency Medicine 2019;26(8):940–3. https://doi.org/10.1111/acem.13811.

Update

Seizure: European Journal of Epilepsy
Volume 80, Issue , August 2020, Page 282

DOI: https://doi.org/10.1016/j.seizure.2020.05.021

Seizure: European Journal of Epilepsy 80 (2020) 282

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Corrigendum to "Medical management of status epilepticus: Emergency room to intensive care unit" [Seizure: Eur. J. Epilep. 75 (2020) 145–152]

Ania A. Crawshaw[a], Hannah R. Cock[b,*]

[a] Specialist Trainee Neurology, Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, London, UK
[b] Professor of Epilepsy & Medical Education, Consultant Neurologist, Atkinson Morley Regional Neuroscience Centre, St George's University Hospitals NHS Foundation Trust, and Institute of Medical & Biomedical Education, St George's University of London, London, UK

The authors regret a mistake in the wording of the fourth of their article's Highlights. The corrected Highlight is as follows:

- Valproate and levetiracetam are recommended and may be preferable to phenytoin

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.seizure.2019.10.006
* Corresponding author.
E-mail address: hannahrc@sgul.ac.uk (H.R. Cock).

https://doi.org/10.1016/j.seizure.2020.05.021

1059-1311/ © 2020 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.